REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested. Claims 1-30 are in this case. Claims 1-30 have been rejected. Claims 1, 6, 7, 11, 16, 17, 20, 25, 26, 28 and 29 have now been amended.

The specification was also amended on pages 50, 51, 52, 112 and 117.

Election/Restrictions

The Examiner has objected to claims 1, 6, 7, 9, 10, 11, 16, 17, 20, 25, 26, 28 and 29 as containing nonelected subject matter (i.e. SEQ ID NOs: 13, 14, 42, 43, and 44).

Claims 1, 6, 7, 9, 10, 11, 16, 17, 20, 25, 26, 28 and 29 have been amended to delete references to nonelected subject matter. New claim 31 has been added.

Information Disclosure Statement

An Information Disclosure Statement in accordance with 37 CFR 1.98(b) is attached.

Rejections over 35 USC 112

The Examiner has rejected claims 1, 3, 8, 10, 11, 13, 18, 19, 20, 22, 27, 28, 29 and 30 under 35 USC 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the relevant art to make and use the invention commensurate in scope with these claims.

Specifically, the Examiner states that the specification, while being enabling for a polynucleotide fragment comprising a polynucleotide sequence encoding a polypeptide of amino acid sequence SEQ ID NO:10, does not reasonably provide enablement for any polynucleotide fragment comprising a polynucleotide sequence encoding a polypeptide which shares 70% homology with SEQ ID NO:10, such that one of ordinary skill in the art would be forced to perform undue experimentation in order to fulfill the invention as claimed.

The rejections of the Examiner are respectfully traversed.

On page 39, lines 11-17, a description is provided of sequence analysis and alignment being performed with the sequence analysis software package developed by the Genetic Computer Group (GCG) at the University of Wisconsin. This description

is sufficient to determine how the percentage homologies were obtained, because this package performs an alignment between sequences. The exact nature of the alignment with regard to whether gaps are introduced, for example, may differ according to the setting of the parameters However, when overall homologies are being discussed, as in this instance, the percentage of such homology does not change radically according to different parameters that are chosen. This is because percentage homology is a global measure of similarity between two sequences, which is not significantly affected by local aspects of sequence alignment. However, the choice of different parameters has a great effect on local features of the sequence alignment, but has a much reduced effect (if any) on the global percentage homology. Thus, the description provided in the parent application is certainly sufficient to teach one of skill in this particular art (protein sequence alignment) how to determine the global measure of homology between two sequences.

This description of how to determine homology between two sequences has been incorporated from the parent application into the present Application as previously described.

Applicant therefore feels that these arguments overcome the Examiner's rejections in this regard.

Furthermore, page 56, lines 3-18 clearly describe use of the amino acid sequence of human heparanase to search for homologous sequences in DNA and protein databases, enabling identification of candidate amino acids that participate in the heparanase active site. Lines 11-13 refer to 81% homology between deduced amino acid sequences from mouse and human *hpa* genes. Homology searches using computer servers and various databases are described on page 83, bridging page 84, lines 1-2.

Page 37, lines 12-22 describes a preparation comprising a recombinant protein, in which the protein includes a polypeptide encoded by a polynucleotide capable of inducing heparanase activity after transfection into a cell, in which the cell is characterized by lacking such heparanase activity before transfection. Applicant feels that this recitation includes a clear structure-function relationship, given the recitation of the polynucleotide that is capable of inducing heparanase activity.

The Examiner contends that one of ordinary skill in the art would not know which changes in the polypeptide sequence could be made while preserving heparanase function. Applicant notes that the present Application clearly teaches an

assay for heparanase activity, as described on p. 74, line 8 to the end, bridging to p.75, lines 1-3. Such an assay could easily be used by one of ordinary skill in the art to determine which proteins having a sequence that falls within the definition of at least 70% homology in the claim also have heparanase activity. A definition of "heparanase activity" is also provided on p. 57, lines 15-20.

The specification at page 72, lines 4 to end, spanning page 73, lines 1-6 describes purification and characterization of heparanase with a purification procedure initiated with Heparin-Sepharose chromatography, followed by gel filtration and pooling of active column fractions, wherein a quantity of the protein after the purification correlates with heparanase activity in the pooled active column fractions. Applicant feels that this recitation overcomes the rejections of the Examiner in that the structural limitations of size and also behavior with Heparin-Sepharose chromatography and gel filtration are all included. Determination as to whether a protein falls within the boundaries of the claims may be achieved by this simple assay, such that undue experimentation is not required.

New claim 31 has been added to further clarify this point; recites a recombinant protein being characterized by being about 50 or about 65 kDa, and also being characterized by being capable of being purified with a purification procedure initiated with Heparin-Sepharose chromatography, followed by gel filtration and pooling of active column fractions, wherein a quantity of the protein after the purification correlates with heparanase activity in the pooled active column fractions. Applicant feels that this recitation overcomes the rejections of the Examiner in that the structural limitations of size and also behavior with Heparin-Sepharose chromatography and gel filtration are all included. Furthermore, this claim recites a simple test which can be used to determine whether a recombinant protein falls within the boundaries of the claim, such that undue experimentation is not required. Support can be found throughout the specification, particularly on pages 90-91.

Applicant notes that the revised Guidelines state in footnote 42 that "examples of identifying characteristics include sequence, structure, binding affinity, binding specificity, molecular weight and length.... For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities or antibody cross-reactivity". Applicant feels that these recited limitations clearly fall within these categories of permissible

identifying characteristics, which clearly distinguish the protein of Applicant and which clearly provide structure-function relationships.

Applicant further notes that the definition of "one of ordinary skill in the art" has been held in numerous court cases to depend upon the art in question; in fields such as that of the present invention, clearly the art would indicate that "one of ordinary skill in the art" could actually be a team of Ph.D. level scientists. Such a team could easily perform the above-described assay in the present Application without undue experimentation, in order to determine whether a particular sequence encodes for a heparanase polypeptide.

For purposes of further clarification, Applicant has submitted alignment data in the attached Affidavit, showing the homology (and differences) between human, rat, mouse and chicken heparanase sequences. Some important shared features such as the heparan sulfate binding site are marked. This information further supports Applicant's statements with regard to the ability of one of ordinary skill in the art to readily recognize a heparanase protein as such. Furthermore, Applicant notes that such homology can even be detected in a heparanase protein that has sequence homology of less than 70%; while for the present invention claims recite "at least 70%" homology.

Applicant furthermore notes that the claims do not require *prediction of protein structure from a sequence*, which seems to be the goal of the reference cited by the Examiner, Ngo et al. The claims are sufficiently supported by the demonstration that variation in sequence homology is possible, to the degree recited by the claims; and that a functional, easily performed assay is taught, which enables one of ordinary skill in the art to determine whether a protein is indeed a heparanase. Certainly, locating homologous proteins according to a known sequence is a relatively easy task. After all, the Human Genome Project has used such sequence comparisons to determine the function of a protein having a new sequence, once the sequence of at least one member of that protein's family was known [**Benner et al.** Res Microbiol. 2000 Mar;151(2):97-106; **Bork & Koonin** Nat Genet. 1998 Apr;18(4):313-8]. Such a comparison is a known tool for the average researcher, and was also available to one of ordinary skill in the art at the time of filing of the priority application. The further provision of an assay enables "false positives" to be easily detected.

Thus, Applicant notes that the criteria stated by the Examiner as being raised by *In re Wands* are all answered in this Response and in the present Application, thereby giving positive support to the present claims. In particular:

1) The quantity of experimentation necessary is minimal, and could certainly be performed by one of ordinary skill in the art, particularly given that such an individual could be a team of scientists. It should be noted that many other cases indicate that merely tedious or laborious experimentation is not considered to be "undue", even if a large amount of experimentation is required (see for example *Ex parte* Erlich 3 U.S.P.Q.2d (B.P.A.I. 1982), and *Ex parte* Jackson, 217 U.S.P.Q. (B.P.A.I. 1982), which indicated that quantity of experiments alone is not sufficient to be "undue", as long as the experiments were routine). Indeed, enablement was upheld for patents which required trial and error experimentation (see for example Durel Corp. v. Osram Sylvania Inc., 52 U.S.P.Q.2d (D.Ariz. 1998)).

2) Sufficient guidance is presented to easily determine whether a particular polypeptide is in fact a heparanase, particularly given the described heparanase assay in the present Application, which is sufficiently simple to be easily performed by one of ordinary skill in the art; guidance is also provided to determine the degree of homology which is also explicitly stated in the claims.

3) Working examples are provided of heparanases having different degrees of homology, as well of how to determine such homology.

4) The nature of the invention is quite well known, as heparanases themselves were known, although their sequences were not; it is not correct to present arguments and references which suggest that the claims relate to a generalized, non-specific protein, when in fact they relate to a specific, well-defined and well-characterized family of proteins, which is the heparanase family.

5) The state of the prior art *at the time of filing of the parent of the present Application* clearly indicated that broad homology to a particular sequence could be determined in a well-characterized manner, as for a family of proteins having a defined function, which is the case for heparanase [**Koch-Nolte et al.** Genomics. 1997 Feb 1;39(3):370-6; **Koonin et al.** Proc Natl Acad Sci U S A. 1995 Dec 5;92(25):11921-5].

6) The relative skill of those in the art was already quite high at the relevant time, particularly for a team of skilled scientists, and particularly for comparing

sequences of a family to determine homology [**Seldin MF,** Methods. 1997 Dec;13(4):445-57].

7) As noted above, heparanase protcins belong to a well-characterized family, which has predictable behavior and sequence homologies.

8) The claims are not any broader than the working examples, and are certainly not as broad as the known homology of those sequences that are described in the present Application and the attached affidavit.

Applicant further wishes to point out that in the parent US Application No. 08/922,170, now U.S. Patent No. 5,968,822, Examiner Rebecca E. Prouty agreed to amend the wording of the first claim by Examiner's Amendment to recite 'at least 70% homology' instead of '70% homology'. This amendment was erroneously not entered in the published patent, but it is recited in the claims of the present application as Applicant believes that Examiner Prouty's considerations should apply.

Double Patenting Rejection

The Examiner has rejected claims 1-30 under the judicially created doctrine of non-obviousness type double patenting as being anticipated by U.S. Patent No. 5,968,822.

A terminal disclaimer in compliance with 37 CFR 1.321(c) and which overcomes the Examiner's rejections is enclosed herewith.

For the reasons given above, Applicant feels that claims 1-31 are in condition for allowance. A prompt Notice of Allowance is respectfully requested.

Respectfully submitted,

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